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Claims

What is claimed is:

1. A compound, including enantiomers, stereoisomers, rotamers, tautomers, racemates and prodrug of said compound, and pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound having the general structure shown in Formula I:

$$\mathbb{R}^4$$
 \mathbb{R}^3
 \mathbb{R}^3

Formula I

wherein:

Y is selected from the group consisting of the following moieties: alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino and heterocycloalkylamino, with the proviso that Y maybe optionally substituted with X¹¹ or X¹²;

 X^{11} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl, with the proviso that X^{11} may be additionally optionally substituted with X^{12} ;

X¹² is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido,

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arylureido, halogen, cyano, or nitro, with the proviso that said alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from X¹²;

R¹ is COR⁵ or B(OR)₂, wherein R⁵ is H, OH, OR⁸, NR⁹R¹⁰, CF₃, C₂F₅, C₃F₇, CF_2R^6 , R^6 , or COR^7 wherein R^7 is H, OH, OR^8 , CHR^9R^{10} , or NR^9R^{10} , wherein R⁶, R⁸, R⁹ and R¹⁰ are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $[CH(R^{1'})]_pCOOR^{11}$, $[CH(R^{1'})]_pCONR^{12}R^{13}$, $[CH(R^{1'})]_pSO_2R^{11}, [CH(R^{1'})]_pCOR^{11}, [CH(R^{1'})]_pCH(OH)R^{11},$ CH(R1')CONHCH(R2')COO R11, CH(R1')CONHCH(R2')CONR12R13 CH(R1')CONHCH(R2')R', CH(R1')CONHCH(R2')CONHCH(R3')COO R11, CH(R1)CONHCH(R2)CONHCH(R3)CONR12R13 CH(R1')CONHCH(R2')CONHCH(R3')CONHCH(R4')COO R11, CH(R1')CONHCH(R2')CONHCH(R3')CONHCH(R4')CONR12R13 CH(R1')CONHCH(R2')CONHCH(R3')CONHCH(R4')CONHCH(R5')COO R11 and CH(R1')CONHCH(R2')CONHCH(R3')CONHCH(R4')CONHCH(R5') CONR¹²R¹³, wherein R^{1'}, R^{2'}, R^{3'}, R^{4'}, R^{5'}, R¹¹, R¹², R¹³, and R' are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl;

Z is selected from O, N, CH or CR;

W maybe present or absent, and if W is present, W is selected from C=O, C=S, C(=N-CN), or SO₂;

Q maybe present or absent, and when Q is present, Q is CH, N, P, (CH₂)_p, (CHR)_p, (CRR')_p, O, NR, S, or SO₂; and when Q is absent, M may be present or absent; when Q and M are absent, A is directly linked to L; A is O, CH₂, (CHR)_p, (CHR-CHR')_p, (CRR')_p, NR, S, SO₂ or a bond; E is CH, N, CR, or a double bond towards A, L or G;

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G may be present or absent, and when G is present, G is (CH₂)_p, (CHR)_p, or (CRR')_p; and when G is absent, J is present and E is directly connected to the carbon atom in Formula I as G is linked to;

J maybe present or absent, and when J is present, J is (CH₂)_p, (CHR)_p, or (CRR')_p, SO₂, NH, NR or O; and when J is absent, G is present and E is directly linked to N shown in Formula I as linked to J;

L may be present or absent, and when L is present, L is CH, CR, O, S or NR; and when L is absent, then M may be present or absent; and if M is present with L being absent, then M is directly and independently linked to E, and J is directly and independently linked to E;

M may be present or absent, and when M is present, M is O, NR, S, SO₂, $(CH_2)_p$, $(CHR)_p$ $(CHR-CHR')_p$, or $(CRR')_p$;

p is a number from 0 to 6; and

R, R', R², R³ and R⁴ are independently selected from the group consisting of H; C₁-C₁₀ alkyl; C₂-C₁₀ alkenyl; C₃-C₈ cycloalkyl; C₃-C₈ heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl;

wherein said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally and chemically-suitably substituted, with said term "substituted" referring to optional and chemically-suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamido, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate;

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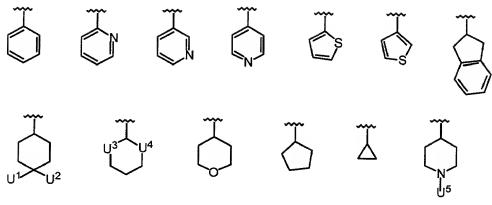
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further wherein said unit N-C-G-E-L-J-N represents a five-membered or six-membered cyclic ring structure with the proviso that when said unit N-C-G-E-L-J-N represents a five-membered cyclic ring structure, or when the bicyclic ring structure in Formula I comprising N, C, G, E, L, J, N, A, Q, and M represents a five-membered cyclic ring structure, then said five-membered cyclic ring structure lacks a carbonyl group as part of the cyclic ring.

- 2. The compound of claim 1, wherein R¹ is COR⁵, and R⁵ is H, OH, COOR⁸, CONR⁹R¹⁰.
- 3. The compound of claim 2, wherein R^1 is $COCONR^9R^{10}$, and R^9 is H, R^{10} is H, R^{14} , $[CH(R^{1'})]_pCOOR^{11}$, $[CH(R^{1'})]_pCONR^{12}R^{13}$, $[CH(R^{1'})]_pSO_2R^{11}$, $[CH(R^{1'})]_pSO_2N$ $R^{12}R^{13}$, $[CH(R^{1'})]_pCOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})$ $CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})$, wherein R^{14} is H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl, alkenyl, alkynyl or heteroaralkyl.
- 4. The compound of claim 3, wherein R¹⁰ is H, R¹⁴, CH(R¹)COOR¹¹, CH(R¹)CH(R¹)COOR¹¹, CH(R¹)CONR¹²R¹³, CH(R¹)CH(R¹)CONR¹²R¹³, CH(R¹)CH(R¹)CH(R¹)COR¹¹, CH(R¹)CH(R¹)CONHCH(R²)COOR¹¹, CH(R¹)CONHCH(R²)COOR¹¹, CH(R¹)CONHCH(R²)CONHCH(R
- 5. The compound of claim 4, wherein R¹ is H.
- 6. The compound of claim 5, wherein R^{11} is H, methyl, ethyl, allyl, *tert*-butyl, benzyl, α -methylbenzyl, α , α -dimethylbenzyl, 1-methylcyclopropyl or 1-methylcyclopentyl;
- 25 R' is hydroxymethyl or CH₂CONR¹²R¹³; R^{2'} is independently selected from the group consisting of:

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wherein:

U¹ and U² maybe same or different and are selected from H, F, CH₂COOH, CH₂COOMe, CH₂CONH₂, CH₂CONHMe, CH₂CONMe₂, azido, amino, hydroxyl, substituted amino, substituted hydroxyl;

U³ and U⁴ maybe same or different and are selected from O and S;

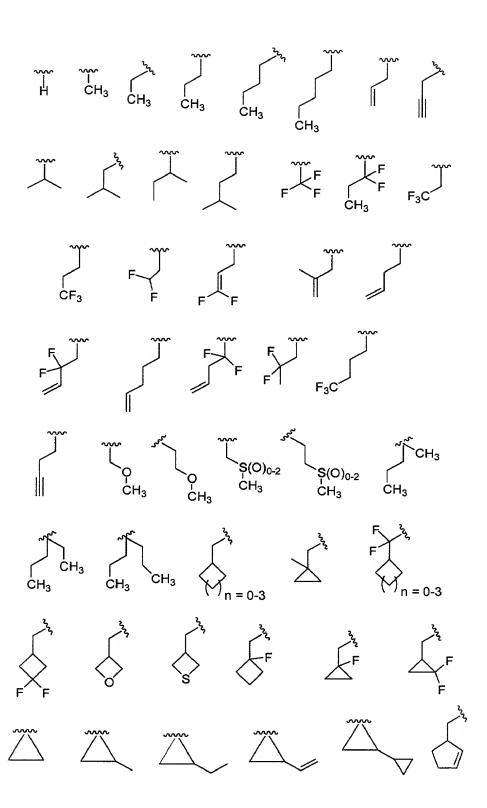
U⁵ is selected from the moieties consisting of alkyl sulfonyl, aryl sulfonyl, heteroalkyl sulfonyl, heteroaryl sulfonyl, alkyl carbonyl, aryl carbonyl, heteroalkyl carbonyl, heteroaryl carbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl or a combination thereof;

heteroarylaminocarbonyl or a combination thereof; and NR¹²R¹³ is selected from the group consisting of:

wherein U⁶ is H, OH, or CH₂OH, and

 R^{14} is selected from the group consisting of: H, Me, Et, *n*-propyl, methoxy, cyclopropyl, *n*-butyl, 1-but-3-ynyl, benzyl, α -methylbenzyl, phenethyl, allyl, 1-but-3-enyl, OMe, cyclopropylmethyl.

7. The compound of claim 2, wherein R² is selected from the group consisting of the following moieties:



8. The compound of claim 7, wherein R³ is selected from the group consisting of:

$$H_3$$
C H_3

wherein R^{31} = OH or O-alkyl;

Y¹⁹ is selected from the following moieties:

and Y²⁰ is selected from the following moieties:

9. The compound of claim 8, wherein R³ is selected from the group consisting of the following moieties:

$$CH_{3} \xrightarrow{} CH_{3} \xrightarrow{$$

- 10. The compound of claim 9, wherein Z is N and R^4 is H.
- 11. The compound of claim 10, wherein W is C=O.

12. The compound of claim 11, wherein Y is selected from the following moieties:

wherein:

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Y¹¹ is selected from H, COOH, COOEt, OMe, Ph, OPh,
NHMe, NHAc, NHPh, CH(Me)₂, 1-triazolyl, 1-imidazolyl,
and NHCH₂COOH;

Y¹² is selected from H, COOH, COOMe, OMe, F, Cl, or Br; Y¹³ is selected from the following moieties:

Y¹⁴ is selected from MeSO₂, Ac, Boc, iBoc, Cbz, or Alloc;

Y¹⁵ and Y¹⁶ are independently selected from alkyl, aryl, heteroalkyl, and heteroaryl;

- Y^{17} is CF₃, NO₂, CONH₂, OH, COOCH₃, OCH₃, OC₆H₅, C₆H₅, COC₆H₅, NH₂, or COOH; and
 - Y^{18} is COOCH₃, NO₂, N(CH₃)₂, F, OCH₃, CH₂COOH, COOH, SO₂NH₂, or NHCOCH₃.
 - 13. The compound of claim 12, wherein Y is selected from the group consisting

10 **of**:

wherein: $Y^{17} = CF_3, NO_2, CONH_2, OH, NH_2, or COOH;$ $Y^{18} = F, COOH,$

14. The compound of claim 13, wherein Y is selected from the group consisting of:

- 15. The compound of claim 14, wherein L and M are absent, and J is directly linked to E.
- 16. The compound of claim 14, wherein L, J and M are absent and E is directly linked to N.
- 5 17. The compound of claim 14, wherein G and M are absent.
 - 18. The compound of claim 14, wherein the moiety:

is
$$\mathbb{R}^{\mathbb{R}^{'}}$$

19. The compound of claim 18, wherein structure <u>a</u> is selected from the following structures:

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20. The compound of claim 18, wherein structure <u>a</u> is:

wherein R²⁰ is selected from the following structures:

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21. The compound of claim 18, wherein structure \underline{a} is:

wherein R^{21} and R^{22} may be the same or different and are independently selected from the following structures:

22. The compound of claim 18, wherein structure \underline{a} is selected from the following structures:

23. The compound of claim 14, wherein:

is
$$\underline{\underline{b}}$$

wherein Q may be present or absent, and if Q is absent, M is directly linked to A.

24. The compound of claim 23, wherein structure <u>b</u> is selected from the

5 following structures:

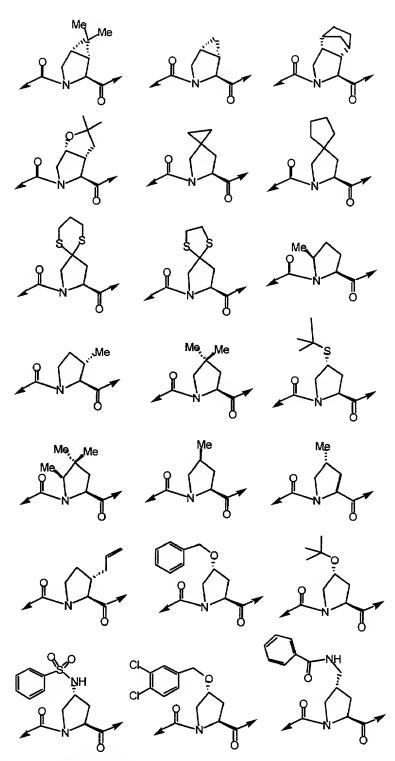
25. The compound of claim 14, wherein:

wherein G and J are independently selected from the group consisting of $(CH_2)_p$, $(CHR)_p$, $(CHR-CHR')_p$, and $(CRR')_p$; A and M are independently selected from the group consisting of O, S, SO₂, NR, $(CH_2)_p$, $(CHR)_p$, $(CHR-CHR')_p$, and $(CRR')_p$; and Q is CH_2 , CHR, CRR', NH, NR, O, S, SO₂, NR, $(CH_2)_p$, $(CHR)_p$, and $(CRR')_p$.

26. The compound of claim 25, wherein structure \underline{c} is selected from the following structures:

27. The compound of claim 14, wherein:

is selected from the following structures:



28. The compound of claim 27, wherein:

is selected from the following structures:

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- 29. A pharmaceutical composition comprising as an active ingredient a compound of claim 1.
- 30. The pharmaceutical composition of claim 29 for use in treating disorders associated with HCV.
- 5 31. The pharmaceutical composition of claim 29 additionally comprising a pharmaceutically acceptable carrier.
 - 32. The pharmaceutical composition of claim 31, additionally containing an antiviral agent.
 - 33. The pharmaceutical composition of claim 32, still additionally containing an interferon.
 - 34. The pharmaceutical composition of claim 33, wherein said antiviral agent is ribavirin and said interferon is α -interferon or pegylated interferon.
 - 35. A method of treating disorders associated with the HCV, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of a compound of claim 1.
 - 36. The method of claim 35, wherein said administration is oral or subcutaneous.
- 37. The use of a compound of claim 1 for the manufacture of a medicament to treat disorders associated with the HCV.
 - 38. A method of preparing a pharmaceutical composition for treating the disorders associated with the HCV, said method comprising bringing into intimate contact a compound of claim 1 and a pharmaceutically acceptable carrier.
- 39. A compound exhibiting HCV protease inhibitory activity, including enantiomers, stereoisomers, rotamers, tautomers, racemates and prodrug of said compound, and pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being selected from the compounds of structures listed below:

 $\begin{array}{l} (\mathsf{R} = \mathsf{t\text{-}butyl}, \, \mathsf{X} = \mathsf{NH}_2) \\ (\mathsf{R} = \mathsf{lsobutyl}, \, \mathsf{X} = \mathsf{NH}_2) \\ (\mathsf{R} = \mathsf{t\text{-}butyl}, \, \mathsf{X} = \mathsf{OH}) \\ (\mathsf{R} = \mathsf{Trichloroethyl}, \, \mathsf{X} = \mathsf{OH}) \end{array}$

 $(X = O^tBu)$ (X = OH)

(X = OH)(X = O^tBu)

 $(X = NH_2)$

(X = NHMe)

 $(X = NMe_2)$

$$(X = NH_2)$$

$$(X = NH_2)$$

$$(X = NHMe_2)$$

$$(X = NHMe)$$

$$(X = OH)$$

$$(X = O'Bu)$$

 $(X = OH)$
 $(X = NH2)$
 $(X = NMe2)$

(R = t-butyl) (R = Isobutyl)

$$(X = O^tBu)$$

$$(X = OH)$$

 $(X = NH_2)$

 $(X = NMe_2)$

(X = NMeOMe)

$$\begin{array}{c|c} H_3C & CH_3 \\ \hline \\ NH & O \\ NH & CH_3 \\ \hline \\ H_3C & H_3C \\ \hline \\ H_3C & H_3C \\ \end{array}$$

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- 40. A pharmaceutical composition for treating disorders associated with the HCV, said composition comprising therapeutically effective amount of one or more compounds in claim 39 and a pharmaceutically acceptable carrier.
- 5 41. The pharmaceutical composition of claim 40, additionally containing an antiviral agent.
 - 42. The pharmaceutical composition of claim 41, still additionally containing an interferon or PEG-interferon alpha conjugate.
 - 43. The pharmaceutical composition of claim 42, wherein said antiviral agent is ribavirin and said interferon is α -interferon.
 - 44. A method of treatment of a hepatitis C virus associated disorder, comprising administering an effective amount of one or more compounds of claim 39.
 - 45. A method of modulating the activity of hepatitis C virus (HCV) protease, comprising contacting HCV protease with one or more compounds of claim 39.
 - 46. A method of treating, preventing, or ameliorating one or more symptoms of hepatitis C, comprising administering an effective amount of one or more compounds of claim 39.
 - 47. The method of claim 45, wherein the HCV protease is the NS3/NS4a protease.
 - 48. The method of claim 47, wherein the compound or compounds inhibit HCV NS3/NS4a protease.
- 49. A method of modulating the processing of hepatitis C virus (HCV) polypeptide, comprising contacting a composition containing the HCV polypeptide under conditions in which the polypeptide is processed with one or more compounds of claim 39.